L-02-0017
Study 4

Acute Oral Toxicity Study in Rats (970592); March 25, 1998

LABORATORIES & CLINICS GROUP
BIOSCIENCE

REDACTED AS TO TRADE NAMES

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[redacted]

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"ACUTE ORAL TOXICITY STUDY IN RATS"

RBM EXP. No. 970592

Issued on March 25, 1998

SPONSOR

AUSIMONT
Viale S.Pietro, 50/A
20021 BOLLATE (Milano)
Italy

PERFORMING LABORATORY

Istituto di Ricerche Biomediche
"Antoine Marxer" RBM S.p.A.
Via Ribes, 1
10010 - COLLERETTO GIACOSA (Torino)
Italy

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RBM Exp. No. 970592

TITLE OF THE STUDY

"Acute oral toxicity study in rats treated with the test article [redacted]"

PURPOSE OF THE STUDY

The purpose of the study was to evaluate the oral acute toxicity of the test article [redacted].

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This report consists of 36 pages.

Ivrea, March 25, 1998

Dr. Ping Yu
RBM Study Director

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BIOSCIENCE

RBM Exp. No. 970592

FOREWORD

On behalf of **AUSIMONT Viale S.pietro, 50/A. 20021-BOLLATE-Milano-Italy** - Ricerche Biomediche "Antoine Marxer" RBM S.p.A., authorized by the Italian Health Authorities (1-2) to conduct safety studies, has performed an acute toxicity study by oral route in Sprague Dawley Crl: CD(SD) BR rat (RBM- Experiment No. 970592), with the test article:

[redacted]

A sample of the substance used, along with pertinent documentation, is held in sufficient quantity in the RBM archives and is at the disposal of the Ministero della Sanità.

The undersigned declare that the experiment was conducted using the same batch of substance as that of the sample held on file.

For verification by the Ministero della Sanità, the undersigned moreover guarantee the identification and classification of all those materials, documents and recordings used in conducting the experiment, held on file for a period of at least 10 years from the date of this report. Following this time, they will be placed at the disposal of the Sponsor.

Dr. Roberto Maraschin

Scientific Director Recognized by the Italian Health Authorities as Responsible for General Toxicology Experimentation

Dr. Angelo Conz

General Manager of the Istituto di Ricerche Biomediche "Antoine Marxer" , RBM S.p.A.

Ivrea, March 25, 1998

(1): **Pharmaceuticals:**
Authorization dated March 12, 1976 in accordance with "Circolare 73", May 16, 1974

(2): **Chemicals:**
Authorization in accordance with DPR 927/81 (D.M. dated January 7, 1988 published in G.U. No. 12, dated January 16, 1988).

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RBM Exp. No. 970592

QUALITY ASSURANCE STATEMENT

RBM Experiment number: 970592

Study title:

"Acute oral toxicity study in rats treated with the test article [redacted]".

Studies of the type described in this report are conducted in a manner which involves frequent repetition of identical or similar procedures.

In compliance with the Principles of Good Laboratory Practice, at the time of this study, procedure-based inspections were made by the Q.A.U. of critical phases and procedures relevant to this type of study. For the inspection of any given procedure, studies were selected at random. All such inspections were reported promptly to the study director and to facility management.

This study was inspected on:

Dates of inspection/audit	Dates of report to Study Director and Management
January 12, 1998	January 13, 1998
March 24, 1998	March 24, 1998

This report has been audited by the Q.A.U. and was found to be an accurate description of such methods and procedures as were used during the conduct of the study and an accurate reflection of the raw data.

Date of final report audit: March 27, 1998

Enrico Invernizzi
Head of Quality Assurance Unit

Date : March 27, 1998

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RBM MANAGEMENT DECLARATION OF GLP COMPLIANCE

Study No. 970592 entitled :

"Acute oral toxicity study in rats treated with the test article [redacted]"

was performed in compliance with the OECD-GLP in the testing of chemicals, [C(81) 30 (final)], regulations also enforced by the Italian Health Authority [D.M. dated June 26, 1986 as published in G.U. No. 198, dated August 27, 1986 and D.L. January 27, 1992, No. 120 as published in G.U. (Supplement) No. 40, February 18, 1992].

Dr. Ping Yu
RBM Study Director

Dr. Angelo Conz
General Manager of the Istituto di Ricerche Biomediche "Antoine Marxer", RBM S.p.A.

Ivrea, March 27, 1998

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SCIENTISTS INVOLVED IN THE STUDY

STUDY No. 970592

"Acute oral toxicity study in rats treated with the test article [redacted]"

RBM Study Director	Dr. Ping Yu
Scientific Director Toxicology	Dr. Roberto Maraschin
Head of General Toxicology I Unit	Dr. Germano Oberto
Centralized Pharmacy Head	Dr. Rita Bussi
Pharmacy Service Head	Dr. Bruna Piccioli

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RBM Exp. No. 970592

MATERIALS AND METHODS

EXPERIMENTAL DESIGN

RBM Experiment No.: 970592

Test article: [redacted]

Administration route: oral (by gavage)

Duration of treatment period: single administration

Duration of post-treatment observation period: 14 days

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.1) and with Organization for Economic Cooperation and Development Guidelines (section 4, subpart 401, Paris 1981 and subsequent revisions).

TEST SYSTEM

Species, strain and substrain: Sprague Dawley Crl: CD (SD) BR rat

Justification for selection of the test system : the Sprague Dawley rat was chosen as rodent species since it is an appropriate experimental model widely accepted by Health Authorities, with documented susceptibility to a wide range of toxic substances

Number and sex of animals: 5 males /dose at the doses of 53, 82 and 128 mg/kg
5 females at the dose of 53 mg/kg

Supplier:	Charles River Italia S.p.A. Via Indipendenza, 11 22050 CALCO (Lecco) Shipping slips No.s 0014 (January 2, 1998), 597 (January 23, 1998) and 793 (January 30, 1998).
Body weight (at randomization)	Males: 246 - 334 g Females: 199 - 214 g The weight variation of the animals used for the study did not exceed ± 20% of the mean body weight for each sex.
Age (at randomization)	males and females <3 months
Acclimatization:	at least 5 days before the start of the test. Animals were observed daily to ascertain their fitness for the study.
Housing:	5 animals/sex/cage in air-conditioned room. - Temperature: 22°C ± 2 - Relative humidity: 55% ± 10 - Air changes: about 20 / hour filtered on HEPA 99.97% - Light: 12 hour cycle (7 a.m. - 7 p.m.) - Cage size: grill cages 40.5x38.5x18h cm with stainless steel feeder. The waste that dropped through the grill bottom onto removable paper was periodically disposed of.
Animal identification:	by appropriately coloring different areas of the limbs. Cage card gave experiment number, dosage group, sex and date of administration.
Diet:	GLP 4RF21 top certificate pelleted diet produced by Charles River Italia's feed licencee Mucedola S.r.l., Settimo Milanese. The declared contents, on the label, on dry matter basis (moisture 12%), were: crude protein 18.50% crude fat 3.00% crude fiber 6.00% crude ash 7.00%

The diet was supplemented by the Producer with vitamins and trace elements. The Producer supplies a certificate of analysis for nutrients and contaminants, the levels of which are within the limits proposed by EPA-TSCA (44FR:44053-44093, July 26, 1979).
RBM has the animal feed re-analyzed at least twice a year for bacterial contamination.
The diet was available "ad libitum" to the animals.

Water: from the municipal water main system.
Water is filtered and distributed "ad libitum" to the animals by an automatic valve system.
Periodically drinking water is analyzed for microbial count, heavy metals, other contaminants (e.g. solvents, pesticides) and other chemical and physicals characteristics. The accepted limits of quality of the drinking water were those defined in EEC directive 80/778

Contaminants that might interfere with the objectives of the study were not expected to be present in diet or drinking water.

TEST ARTICLE CHARACTERIZATION

Identification:	[redacted]
Batch:	19387/20
Characteristics:	white solid
Manufacturing date:	December, 1997
Expiry date:	December, 2000
Storage conditions:	at room temperature

VEHICLE CHARACTERIZATION

Deionized water

TEST ARTICLE FORMULATE PREPARATION

When necessary, an exact amount of test article was weighed in a suitable graduated container and was made up to final volume with vehicle to obtain the concentration required.

Formulates were given to rats within two hours of the preparation.

TEST DESCRIPTION

Administration route: oral (by gavage)

Reason for selection of administration route: possible ingestion by humans

Experimental design:

Dose* mg/kg	Treated animals	Treatment date	Final killing
128	5 males	February 3, 1998	Found dead
82	5 males	February 17, 1998	March 3, 1998
53	5 males	February 27, 1998	March 13, 1998
53	5 females	March 4, 1998	March 18, 1998

* The dose levels were defined on the basis of a preliminary study.

Administration method: The volumes to be administered were 10 ml/kg on the basis of body weight taken just before treatment. The administration was done by gavage to rats which had been fasted about 16 hours. Feed was returned to the rats about three hours after the test article administration.

Observation period: 14 days after administration

Observation of clinical signs and mortality: at 15 and 30 minutes, 2, 4 and 6 hours on the first day after the administration (day 1) and then twice a day up to termination of the observation period

Body weight: twice pre-trial (at randomization and on day 1 just before administration) and on days 3, 8 and 14. On day 1 the animals were weighed after a 16-hour fasting period.

Gross pathology:	on all animals which died during the observation period and on animals killed (fasted overnight) by excision of the femoral arteries, after i.p. overdosage anesthesia with 5% sodium pentobarbital, at the end of the observation period
Histology:	portions of any abnormal entities found in any of the necropsied animals were collected. The tissue samples were fixed and preserved in 10% buffered formalin. Histologic examination was not performed.
LD_{50} and its statistical limits:	LD_{50} was calculated by the method of the Probit (Bliss - Finney) - A.P. Rosiello et al., J. Tox. and Env. Health, 3: 797-809, 1977.

RECORD FILING

The protocol, a reserve sample of the batch of the test article used, the raw data bound in a register numbered 970592/1, the specimens, the final report and all other documents pertinent to the conduct of this study, including records and reports of maintenance, cleaning, calibration and inspection of equipment, analysis of diet and water are filed at RBM premises for ten years from the issue date of this report and then sent to the Sponsor.

PROCEDURAL DETAILS

The study was conducted in accordance with the procedures described in the RBM Standard Operating Procedures (SOP's) collection.

Protection of animals used in the experiment is in accordance with Directive 86/609/EEC, enforced by the Italian D. L. No. 116 of January 27, 1992.

Physical facilities and equipment for accommodation and care of animals are in accordance with the provisions of EEC Council Directive 86/609.

The Institute is fully authorized by Competent Veterinary Health Authorities.

RESULTS

CLINICAL OBSERVATIONS

MORTALITY *(TABLE 1)*

The mortality which occurred at the various doses is given below:

Dose (mg/kg)	53	82	128
Treated animals	5M+5F	5M	5M
Mortality	0	3M	5M
Total (%)	0%	60%	100%

The deaths occurred within 9 days of dosing, with the first case observed on day 6 after administration in the 128 mg/kg group.

The LD_{50} was calculated to be 82.8 mg/kg with 95% confidence limits of 68.9 - 99.5 mg/kg.

CLINICAL SIGNS *(TABLE 2 AND APPENDIX 1)*

At the higher doses tested (82 and 128 mg/kg) the compound induced delayed clinical changes including: sedation or hypoactivity, piloerection and hunched posture. These changes were detected starting days 6-8 after dosing.

Recovery was achieved at the end of the observation period in the surviving animals.

No changes of note were seen in animals of the lowest dose group (53 mg/kg).

BODY WEIGHT *(APPENDIX 2)*

Decrease in body weight or retarted growth was found in animals given the two higher doses (82 and 128 mg/kg) mainly during the first week of the observation period.

No effects on the body weight growth was observed in animals of the 53 mg/kg group.

POST-MORTEM EXAMINATION

GROSS PATHOLOGY *(TABLE 3 AND APPENDIX 3)*

At the necropsy of animals which died before the end of the observation period, the main macroscopic finding was marked or moderate liver paleness in all animals. Moreover, stomach congestion, kidney medulla congestion and decreased size of spleen were seen in some animals.

No appreciable findings were detected at the gross examination in animals which were sacrificed at the end of the observation period.

SUMMARY AND CONCLUSIONS

Experimental data from a toxicity study in which Sprague Dawley Crl:CD(SD) BR rats were treated by oral route with the test article [redacted] are given in this report.

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.1) and with Organization for Economic Cooperation and Development Guideline (section 4, subpart 401, Paris 1981 and subsequent revisions).

The test article was administered as a solution in deionized water at the doses of 53, 82 and 128 mg/kg to groups of 5 males/dose and at the dose of 53 mg/kg also to 5 females for confirmation in the other sex . The volume of administration was 10 ml/kg.

All rats were treated after a 16-hour fasting period. The day of treatment was considered day 1 of the study. The animals were weighed twice before treatment (at randomization and on day 1 just before treatment) and on days 3, 8 and 14. They were clinically observed for 14 days following the treatment. Macroscopic examination was performed on all animals which died before the end of the study. On day 15 the surviving rats were killed (fasted overnight) by excision of the femoral arteries after i.p. overdosage anesthesia with 5% sodium pentobarbital and were subjected to a thorough autopsy.

The mortality which occurred at the various doses is given below:

Dose (mg/kg)	53	82	128
Treated animals	5M+5F	5M	5M
Mortality Total (%)	0 0%	3M 60%	5M 100%

Deaths occurred within 9 days of dosing, with the first case observed on day 6 after administration in the 128 mg/kg group.

The LD_{50} was calculated to be 82.8 mg/kg with 95% confidence limits of 68.9 - 99.5 mg/kg.

At the higher doses tested (82 and 128 mg/kg) the compound induced delayed clinical changes including sedation or hypoactivity, piloerection and hunched posture. These changes were detected starting days 6-8 after dosing. Recovery was achieved by the end of the observation period in the surviving animals.

No changes of note were seen in animals of the lowest dose group (53 mg/kg).

Depression in body weight growth was found in animals given the two higher doses (82 and 128 mg/kg) mainly during the first week of the observation period.

No effects on the body weight growth was observed in animals of the 53 mg/kg group.

At the necropsy of animals which died before the end of the observation period, the main macroscopic finding was marked or moderate liver paleness.

No appreciable findings were found in animals at the final killing.

In conclusion, the **LD_{50}** of the test article [redacted], when administered to rats as a single dose by oral route, was **82.8 mg/kg (95% confidence limits: 68.9-99.5 mg/kg)**. The compound induced delayed toxicity (liver was mainly involved) in animals given the higher doses.

Dr. Ping Yu

RBM Study Director

March 25, 1998

Dr. Roberto Maraschin

Scientific Director Recognized by the Italian Health Authorities as Responsible for General Toxicology Experimentation

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GROUP DATA

Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

TABLE 1. - Mortality and LD50 calculation (p. 1)

Males - Females

Dose (mg/kg)		53	82	128
Treated animals		10	5	5
Day	6	0	0	1
	7	0	0	2
	8	0	0	1
	9	0	3	1
Total no.	(day 14)	0	3	5
Total (%)		.0%	60.0%	100.0%

Median lethal dose (LD50) = 82.79

95% confidence limits = 68.92 - 99.46

Slope (SE) = 3.19 .78

Heterogeneity P = .557 NS

Linear regression y =-9.1040+3.1936x

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

TABLE 2. - Clinical signs (maximum daily frequency) (p. 1)
(no. of animals affected, from-to)

	Males		
Dose (mg/kg)	53	82	128
no. of treated animals	5	5	5
Death	-	3 9d	5 6d- 9d
Sedation	-	1 8d- 8d	2 6d- 6d
Hypoactivity	-	-	2 7d- 8d
Piloerection	-	3 8d-12d	4 6d- 8d
Hunched posture	-	3 8d-12d	3 6d- 8d
Recovery	-	2 13d	-

- (not observed) from-to (first-last observation in one or more animals)
Time : d (days)

Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

TABLE 2. - Clinical signs (maximum daily frequency) (p. 2)
(no. of animals affected, from-to)

	Females
Dose (mg/kg)	53
no. of treated animals	5
No clinical signs	5 30m-14d

from-to (first-last observation in one or more animals)
Time : m (minutes) d (days)

Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

TABLE 3. - Gross pathology examination (p. 1)
(no. of cases, mean severity, %)

Dead or agonal sacrificed an. Males

Dose (mg/kg)	53	82	128
no. of animals	0	3	5
no. of animals without appreciable lesions	0	0	0
Kidneys			
medulla, congestion	-	3(2.0) 100.00%	3(2.0) 60.00%
Liver			
pale	-	3(2.0) 100.00%	5(2.8) 100.00%
Spleen			
decreased size	-	2(2.0) 66.67%	3(2.0) 60.00%
Stomach			
congestion	-	3(2.0) 100.00%	2(2.0) 40.00%

- (not examined)
Severity : 0(very slight) 1(slight) 2(moderate) 3(severe)

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

TABLE 3. - Gross pathology examination (p. 2)
(no. of cases, mean severity, %)

Final killing	Males		
Dose (mg/kg)	53	82	128
no. of animals	5	2	0
no. of animals without appreciable lesions	5	2	0

Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

TABLE 3. - Gross pathology examination (p. 3)
(no. of cases, mean severity, %)

Final killing	Females
Dose (mg/kg)	53
no. of animals	5
no. of animals without appreciable lesions	5

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APPENDICES

Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 1. - Clinical signs incidence (p. 1)
(no. of animals affected)

Dose (mg/kg) 53

Cage # 9M	Day	1				2		3		4		5		6		7		8		9		10		11		12		13		14	
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
No clinical signs		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Cage # 10F	Day	1				2		3		4		5		6		7		8		9		10		11		12		13		14	
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
No clinical signs		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Time: m (minutes) h (hours) M (morning) A (afternoon)

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 1. - Clinical signs incidence (p. 2)
(no. of animals affected)

Dose (mg/kg) 82

Cage # 7M	Day	1				2		3		4		5		6		7		8		9		10		11		12		13		14	
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
Death																				3											
No clinical signs		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	1	1									2	2	2	2
Sedation																		1	1												
Piloerection																		3	3	2	2	2	2	2	2	2	2				
Hunched posture																		3	3	2	2	2	2	2	2	2	2				

Time: m (minutes) h (hours) M (morning) A (afternoon)

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 1. - Clinical signs incidence (p. 3)
(no. of animals affected)

Dose (mg/kg) 128

Cage # 5M	Day	1				2		3		4		5		6		7		8		9
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M
Death														1		2		1		1
No clinical signs		5	5	5	5	5	5	5	5	5	5	5	5							
Sedation														2	2					
Hypoactivity																2	2	1	1	
Piloerection														4	4	2	2	1	1	
Hunched posture														3	3	2	2	1	1	

Time: m (minutes) h (hours) M (morning) A (afternoon)

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 2. - Body weight (g) (p. 1)
(individual)

Dose (mg/kg) 53

Animal #		41M	42M	43M	44M	45M	46F	47F	48F	49F	50F
Week	day										
	0	246	247	246	246	248	200	214	204	199	199
1	1	223	225	222	220	220	189	194	189	187	186
1	3	240	243	240	237	236	203	229	205	202	203
2	8	268	266	250	268	245	217	233	211	214	211
2	14	359	347	333	350	309	236	258	233	238	234

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 2. - Body weight (g) (p. 2)
(individual)

Dose (mg/kg) 82

Animal #		31M	32M	33M	34M	35M
Week	day					
	0	334	334	300	334	334
1	1	318	309	271	324	322
1	3	310	310	261	346	312
2	8	232	255	208	280	266
2	14		343			369

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 2. - Body weight (g) (p. 3)
(individual)

Dose (mg/kg) 128

Animal #		21M	22M	23M	24M	25M
Week	day					
	0	289	270	250	281	299
1	1	265	248	229	258	267
1	3	250	245	222	256	265
2	8		169			

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 3. - Gross pathology examination (p. 1)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 82

An#	Death day/code#	TISSUE	Gross observations
31M	9 M2	Kidneys	medulla, congestion, diffuse, moderate
		Liver	pale, diffuse, moderate
		Spleen	decreased size, diffuse, moderate
		Stomach	congestion, diffuse, moderate
33M	9 M2	Kidneys	medulla, congestion, diffuse, moderate
		Liver	pale, diffuse, moderate
		Stomach	congestion, diffuse, moderate
34M	9 M2	Kidneys	medulla, congestion, diffuse, moderate
		Liver	pale, diffuse, moderate
		Spleen	decreased size, diffuse, moderate
		Stomach	congestion, multifocal, moderate

Death code : M2(Natural death)

Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 3. - Gross pathology examination (p. 2)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 128

An#	Death day/code#	TISSUE	Gross observations
21M	7 M2	Liver	pale, diffuse, severe
		Spleen	decreased size, diffuse, moderate
22M	9 M2	Kidneys	medulla, congestion, diffuse, moderate
		Liver	pale, diffuse, moderate
		Stomach	congestion, diffuse, moderate
23M	8 M2	Liver	pale, diffuse, severe
		Spleen	decreased size, diffuse, moderate
		Stomach	congestion, diffuse, moderate
24M	6 M2	Kidneys	medulla, congestion, diffuse, moderate
		Liver	pale, diffuse, severe
		Spleen	decreased size, diffuse, moderate
25M	7 M2	Kidneys	medulla, congestion, diffuse, moderate
		Liver	pale, diffuse, severe

Death code : M2(Natural death)

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 3. - Gross pathology examination (p. 3)
(individual)

Final killing

Dose (mg/kg) 53

An#	Death day	T I S S U E	Gross observations
41M	15	General observation	no macroscopically appreciable lesions
42M	15	General observation	no macroscopically appreciable lesions
43M	15	General observation	no macroscopically appreciable lesions
44M	15	General observation	no macroscopically appreciable lesions
45M	15	General observation	no macroscopically appreciable lesions
46F	15	General observation	no macroscopically appreciable lesions
47F	15	General observation	no macroscopically appreciable lesions
48F	15	General observation	no macroscopically appreciable lesions
49F	15	General observation	no macroscopically appreciable lesions
50F	15	General observation	no macroscopically appreciable lesions

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Test article: [redacted]
Title : Acuate oral toxicity study in rats
RBM exp. : 970592

APPENDIX 3. - Gross pathology examination (p. 4)
(individual)

Final killing

Dose (mg/kg) 82

An#	Death day	T I S S U E	Gross observations
32M	15	General observation	no macroscopically appreciable lesions
35M	15	General observation	no macroscopically appreciable lesions